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[54] PHARMACEUTICAL COMPOSITION
CONTAINING DILTIAZEM AND
ANGIOTENSIN-CONVERTING ENZYME
INHIBITOR

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[63] Continuation-in-part of Ser. No. 115,315, Nov. 2, 1987,
abandoned.

[30] Foreign Application Priority Data

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[52] U.S. Cl. 514/211; 514/423

[58] Field of Search 514/211, 423

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[57] ABSTRACT

Compositions of diltiazem and angiotensin-converting
enzyme inhibitor useful for the treatment of hyperten-
sion, cardiac insufficiency and coronary insufficiency.

2 Claims, No Drawings

PHARMACEUTICAL COMPOSITION
CONTAINING DILTIAZEM AND
ANGIOTENSIN-CONVERTING ENZYME
INHIBITOR

This application is a continuation-in-part of applica-
tion Ser. No. 115,315 filed Nov. 2, 1987, now aban-
doned.

BACKGROUND OF THE INVENTION

The present invention relates to pharmaceutical com-
positions containing diltiazem and an angiotensin-con-
verting enzyme inhibitor useful in the treatment of hy-
pertension.

Hypertension is a field in which polytherapy is en-
countered extremely frequently.

Calcium inhibitors occupy a position of increasing
importance in the field of hypertension. They are being
recommended as a first line treatment in elderly hyper-
tensive patients, who are known to be very numerous. It
appears, however, that combinations of calcium inhibi-
tors with diuretics and/or β -blockers are not com-
pletely satisfactory.

According to indication, diltiazem is beneficial in that
it is well tolerated, and is currently gaining as leader in
the field of angina pectoris; however, its relatively weak
peripheral vasodilatory action could constitute a handi-
cap.

Angiotensin-converting enzyme inhibitors have been
found to provide a component having beneficial periph-
eral vasodilatory action.

SUMMARY OF THE INVENTION

The subject of the present invention is pharmaceuti-
cal compositions containing diltiazem and an angioten-

pressure transducer for microcirculatory studies. J.
Appl. Physiol. 27: 422,425, 1969) permits continuous
intra-arterial perfusion of isotonic sodium chloride solu-
tion (0.1 ml/kg/min) throughout the experiment, this
perfusion preventing possible coagulation without edi-
fying the animals' blood pressure or heart rate. The
blood pressure is recorded continuously on a Grass
polygraph (model 7D) using a Grass preamplifier
(model 7P1).

The results of the tests cited hereinafter have enabled
the useful properties of the invention in the treatment of
hypertension.

The subject of the invention is compositions having
usefulness in the treatment of hypertension, cardiac
insufficiency and coronary insufficiency characterized
in that they contain a combination of diltiazem and an
angiotensin-converting enzyme inhibitor.

The experiments are described in the following exam-
ples.

EXAMPLE 1

After a stabilization period of approximately 2 hours,
three different groups of animals receive orally a dose
of diltiazem (25 mg/kg), a dose of the angiotensin-con-
verting enzyme inhibitor, captopril (20 mg/kg) or a
combination of the two doses of diltiazem and captopril.
The mean arterial pressure (MAP) is measured before
the administration of the therapeutic agents, and then at
several times during the 4 hours following the adminis-
tration of one of the compounds or the combination of
the two therapeutic agents.

The results are given in the form of mean decreases in
blood pressure with respect to the base-line pressure.

The results obtained for the compounds administered
alone and for the combination of diltiazem and captopril
are given in the following table.

Compound	dose mg/kg p.o.	n	Initial MAP mmHg	Δ MAP (mmHg)					
				0,5 h	1 h	1,5 h	2 h	3 h	4 h
diltiazem (dilt)	25,0	5	209 \pm 4,3	-15 \pm 3,2	-9 \pm 2,5	-4 \pm 3,3	-2 \pm 5,8	0 \pm 5,2	1 \pm 5,8
captopril (cap)	20,0	5	203 \pm 4,1	-19 \pm 2,5	-17 \pm 2,6	-19 \pm 2,5	-19 \pm 2,9	-18 \pm 1,2	-13 \pm 2,6
dilt + cap	25/20	6	214 \pm 3,8	-48 \pm 3,8*	-41 \pm 3,3*	-38 \pm 2,1*	-32 \pm 4,8	-24 \pm 5,4	-23 \pm 5,9

*significantly different from the sum of the effects of diltiazem and captopril given alone.

sin-converting enzyme for the treatment of hyperten-
sion, cardiac insufficiency and coronary insufficiency.

Examples of the angiotensin-converting enzyme in-
hibitors are: captopril, enalapril, alacepril, enalaprilat,
fentiapril, lisinopril, ramipril, perindopril, cilazapril,
fosinopril, pivopril, quinilapril and zofenopril.

The action of the combinations of diltiazem and angio-
tensin-converting enzyme inhibitors on hypertension
have been studied on unanesthetized spontaneously
hypertensive rats (SHR).

The test used in the study is as follows: A catheter is
permanently installed in the caudal artery of 12-month
old male SHR's under mild ether anaesthesia. The ani-
mals are then placed in individual cages which enable
them to move freely, and the catheters are connected to
Statham P23Gc pressure cells. A special device (Lavas-
seur J. E., Funk F. C., Patterson J. L. Jr., Physiological

EXAMPLE 2

After a stabilization period of approximately 2 hours,
different groups of animals received orally diltiazem (25
mg/kg) or placebo (distillated water +0.2 % tween) 10
min after intra-arterial administration of saline or of the
angiotensin-converting enzyme inhibitor, enalapril (1
mg/kg). The mean arterial pressure (MAP) is measured
before the administration of the therapeutic agents, and
then at several times during the 4 hours following the
administration of one of the compounds or the combina-
tion of the two therapeutic agents.

The results are given in the form of mean decreases in
blood pressure with respect to the base-line pressure.

The results obtained for the compounds administered
alone and for the combination of diltiazem and enalapril
are given in the following table.

Compound	Initial MAP	Δ MAP (mmHg)					
		0,5 h	1 h	1,5 h	2 h	3 h	4 h
saline + DTZ ₂₅ (n = 8)	194 \pm 4,6	-26 \pm 2,6	-18 \pm 1,9	-13 \pm 2,3	-7 \pm 1,9	-4 \pm 1,8	-1 \pm 1,5

-continued

Compound	Initial MAP	Δ MAP (mmHg)					
		0,5 h	1 h	1,5 h	2 h	3 h	4 h
ENA ₁ + PLACEBO (n = 4)	194 ± 11,4	-9 ± 4,3	-13 ± 3,2	-9 ± 1,3	-5 ± 2,0	-4 ± 1,3	-3 ± 1,4
ENA ₁ + DTZ ₂₅ (n = 8)	190 ± 4,1	-40 ± 3,3	-36 ± 2,6	-35* ± 2,3	-33* ± 2,7	-31* ± 3,0	-24* ± 2,7

*significantly different from the sum of the effects of diltiazem and enalapril given alone.
ENA₁ = enalapril (1 mg/kg i.a.)
DTZ₂₅ = diltiazem (25 mg/kg p.o.)

EXAMPLE 3

After a stabilization period of approximately 2 hours, different groups of animals receive orally diltiazem (25 mg/kg) or placebo (distillated water +0.2% tween) 30 mn after intra-arterial administration of saline or of the angiotensin-converting enzyme inhibitor, fosinopril (10 mg/kg).

The mean arterial pressure (MAP) is measured before the administration of the therapeutic agents, and then at several times during the 5 hours following the administration of one of the compounds or the combination of the two therapeutic agents.

The results are given in the form of mean decreases in blood pressure with respect to the base-line pressure.

The results obtained for the compounds administered alone and for the combination of diltiazem and fosinopril are given in the following table.

Compound	MPA Initial Data	Δ MPA (mmHg)						
		0,5 h	1 h	1,5 h	2 h	3 h	4 h	5 h
SALINE + DTZ ₂₅ (n = 6)	193 ± 4,4	-22 ± 4,2	-11 ± 4,0	-9 ± 3,3	-3 ± 3,8	-2 ± 4,0	-2 ± 4,4	-2 ± 4,2
FOS ₁₀ + PLACEBO (n = 3)	195 ± 7,6	10 ± 5,8	8 ± 3,3	7 ± 4,4	7 ± 4,4	5 ± 2,9	-3 ± 6,0	-2 ± 3,2
FOS ₁₀ + DTZ ₂₅ (n = 5)	196 ± 4,3	-22 ± 3,4	-25* ± 4,2	-32* ± 4,1	-35* ± 5,0	-36* ± 4,3	-41* ± 4,0	-43* ± 4,1

*significantly different from the sum of the effects of diltiazem and fosinopril given alone.
DTZ₂₅ = diltiazem (25 mg/kg p.o.)
FOS₁₀ = fosinopril (10 mg/kg i.a.).

The results show that the combinations of diltiazem and captopril, diltiazem and enalapril, diltiazem and fosinopril, produce a significantly greater antihypertensive effect than the sum of the effects brought about by each of the compounds administered separately.

There is hence, a synergy between the antihypertensive effects of diltiazem and of the angiotensin-converting enzyme inhibitors mentioned above, per unit dose.

Pharmaceutical compositions of the invention may be presented in any form suitable for oral or parenteral administration, in combination with any suitable excipient.

Each unitary dose of the pharmaceutical compositions of the invention contains from 10 to 360 mg of

diltiazem and 1 to 100 mg of an angiotensin-converting enzyme inhibitor mentioned above.

The dosage which can be administered daily is such that from 10 to 240 mg diltiazem and from 1 to 100 mg of one of the angiotensin-converting enzyme inhibitors are administered.

What is claimed is:

1. A pharmaceutical composition containing a combination of 10-360 mg of diltiazem and 1-100 mg of an angiotensin-converting enzyme inhibitor, enalapril useful for the treatment of hypertension, cardiac insufficiency, and coronary insufficiency, such that the anti-hypertensive effect observed upon combined administration of diltiazem and said angiotensin-converting enzyme inhibitor is greater than the sum of the individual anti-hypertensive effects observed upon the separate administration of diltiazem and said angiotensin-converting enzyme inhibitor alone.

2. A method for treatment of hypertension, cardiac insufficiency or coronary insufficiency comprising administering to a subject suffering therefrom a pharmaceutical composition containing a combination of 10 to 360 mg of diltiazem and 1 to 100 mg of an angiotensin-converting enzyme inhibitor, enalapril, such that the anti-hypertensive effect observed upon administration of the combined administration of diltiazem and said angiotensin-converting enzyme inhibitor is greater than the sum of the individual anti-hypertensive effects observed upon the separate administration of diltiazem and said angiotensin-converting enzyme inhibitor alone.

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